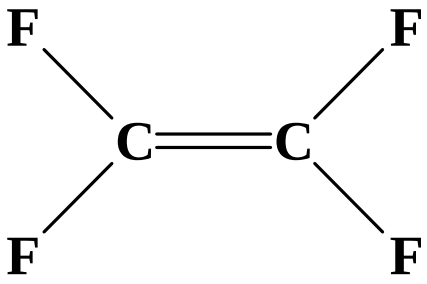
ABSTRACT



TETRAFLUOROETHYLENE

CAS No. 116-14-3

Chemical Formula: C_2F_4 Molecular Weight: 100.02

Synonyms: Perfluoroethylene; tetrafluoroethene; 1,1,2,2-tetrafluoroethylene; TFE

Tetrafluoroethylene is used in the production of polytetrafluoroethylene (Teflon®) and other polymers. Tetrafluoroethylene was nominated by the National Cancer Institute for toxicity and carcinogenicity studies based on the potential for human exposure to the chemical due to the large production volume and on the lack of adequate data for tetrafluoroethylene in the literature. Male and female F344/N rats and B6C3F$_1$ mice were exposed to tetrafluoro ethylene (98% to 99% pure) by whole body inhalation exposure for 16 days, 13 weeks, or 2 years. Genetic toxicity studies were conducted in mouse peripheral blood erythrocytes.

16-DAY STUDY IN RATS

Groups of five male and five female F344/N rats were exposed to 0, 312, 625, 1,250, 2,500, or 5,000 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week for a total of 12 exposures during a 16-day period. All rats survived to the end of the study. The final mean body weights and body weight gains of males and females exposed to 5,000 ppm were significantly less than those of the controls. The mean body weight gain of females exposed to 2,500 ppm was also significantly less than that of the controls. There were no exposure-related clinical findings in male or female rats. There were no significant differences in hematology parameters that were considered to be related to tetrafluoroethylene exposure. Absolute and relative kidney weights of all exposed groups of males were significantly greater than those of the controls, as were those of females in the 2,500 and 5,000 ppm groups. The absolute kidney weight of females exposed to 1,250 ppm was also significantly greater than that of the controls. The relative liver weights of all exposed groups of males and the absolute liver weights of males in the 625 and 2,500 ppm groups were significantly greater than those of the controls. Increased incidences of renal tubule degeneration occurred in males and females exposed to 625 ppm or greater; this lesion was located predominantly at the corticomedullary junction. The severity of degeneration increased with increasing exposure concentration and was slightly greater in males than females.

16-DAY STUDY IN MICE

Groups of five male and five female B6C3F$_1$ mice were exposed to 0, 312, 625, 1,250, 2,500, or 5,000 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week for a total of 12 exposures during a 16-day period. All mice survived to the end of the study. Final mean body weights and body weight gains of all exposed groups of mice were similar to those of the controls. There were no exposure-related clinical findings in male or female mice. There were no significant differences in

hematology parameters that were considered to be related to tetrafluoroethylene exposure. The absolute and relative liver weights of females exposed to 5,000 ppm were significantly greater than those of the controls, as was the absolute kidney weight of females in that group and the absolute liver weight of females in the 2,500 ppm group. Renal tubule karyomegaly was observed in male and female mice in the 1,250, 2,500, and 5,000 ppm groups, and the severity of this lesion increased with increasing exposure concentration. Karyomegaly was located predominantly in the inner renal cortex.

13-WEEK STUDY IN RATS

Groups of 10 male and 9 or 10 female F344/N rats were exposed to 0, 312, 625, 1,250, 2,500, or 5,000 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week, for 13 weeks. All rats survived to the end of the study. The final mean body weight and body weight gain of males exposed to 5,000 ppm were significantly less than those of the controls, as was the mean body weight gain of females in this exposure group. There were no clinical findings attributed to exposure to tetrafluoroethylene. Exposure of rats to tetrafluoroethylene resulted in a concentration-dependent normocytic, normochromic, nonresponsive anemia consistent with a secondary hypoproliferative anemia. An exposure concentration-dependent proteinuria also occurred, consistent with renal tubule degeneration observed histopathologically. The absolute and relative liver weights of all exposed groups of males and of females in the 5,000 ppm group were significantly greater than those of the controls. The absolute and relative right kidney weights of males and females exposed to 1,250 ppm or greater and of females in the 625 ppm group were also significantly greater than those of the controls. There were no differences in sperm morphology or vaginal cytology parameters between control and exposed groups of rats. Incidences of renal tubule degeneration in males exposed to 625 ppm or greater and in females exposed to 2,500 or 5,000 ppm were significantly greater than those in the controls. Renal lesions were similar to those observed in the 16-day study and were located predominantly at the corticomedullary junction.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 312, 625, 1,250, 2,500, or 5,000 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week, for 13 weeks. All mice survived to the end of the study. Final mean body weights and body weight gains of all exposed groups of male and female mice were generally similar to those of the controls. There were no clinical findings that were considered to be related to tetrafluoroethylene exposure. Exposure of mice to tetrafluoroethylene resulted in a concentration-dependent normocytic, normochromic, nonresponsive anemia, consistent with a secondary hypoproliferative anemia, and in polyuria. Differences in sperm morphology parameters and estrous cycle lengths were not considered to be exposure related. Incidences of karyomegaly of the renal tubule epithelial cells in male and female mice exposed to 1,250 ppm or greater were significantly greater than those in the controls. Karyomegaly was similar to that observed in the 16-day study and was observed primarily in the inner renal cortex.

2-YEAR STUDY IN RATS

Groups of 60 male rats were exposed to 156, 312, or 625 ppm and groups of 60 female rats were exposed to 312, 625, or 1,250 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week, for 104 weeks, with an observation period of 11 days following the final exposure. Ten male and ten female rats from each exposure group were evaluated at 15 months for organ weights and clinical pathology.

Survival, Body Weights, and Clinical Findings

Survival rates of males in the 625 ppm group and of all exposed groups of females were significantly less than those of the controls. Mean body weights of males exposed to 625 ppm were lower than those of the controls from week 81 until the end of the study, and the mean body weight of 1,250 ppm females was slightly lower than that of the controls at the end of the study. The only clinical finding associated with exposure to tetrafluoroethylene was opacity of the eyes in exposed groups of female rats; this change was observed microscopically as cataracts.

Hematology, Clinical Chemistry, and Urinalysis

At the 15-month interim evaluation, there were no differences in hematology, clinical chemistry, or urinalysis parameters that were considered to be related to tetrafluoroethylene exposure.

Pathology Findings

The absolute and relative kidney weights of males exposed to 625 ppm and females exposed to 1,250 ppm and the absolute kidney weight of females exposed to 625 ppm were significantly greater than those of the controls at the 15-month interim evaluation. At 15 months, renal tubule hyperplasia was observed in one male exposed to 312 ppm and one male and one female exposed to 625 ppm; oncocytic hyperplasia was observed in one female exposed to 1,250 ppm. At the end of the study, incidences of renal tubule adenoma were greater in males and females exposed to 312 ppm or greater than those in the controls. This exposure-related increase was confirmed by examination of step sections (extended evaluations). At the end of the study, the incidences of renal tubule hyperplasia in males exposed to 625 ppm and females exposed to 1,250 ppm were significantly greater than those in the controls. The incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in the extended evaluations and in the standard and extended evaluations (combined) in the 1,250 ppm female group and the 625 ppm male group were significantly greater than those in the controls, and the incidences occurred with significant positive trends. Oncocytic hyperplasia was observed at the end of the study in one male exposed to 312 ppm and in three females exposed to 1,250 ppm. At 15 months and at the end of the study, the incidences of renal tubule degeneration in all exposed groups of males and in females in the 625 and 1,250 ppm groups were greater than those in the controls. Renal tubule degeneration was similar to that observed in the 13-week study and was located predominantly at the corticomedullary junction. The severity of nephropathy generally increased with increasing exposure concentration in male rats at 15 months and 2 years.

The absolute and relative liver weights of females in the 1,250 ppm group and the absolute liver weight of females exposed to 625 ppm were significantly greater than those of the controls at the 15-month interim evaluation. At 2 years, the incidences of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) in males exposed to 312 ppm, the incidences of hepatocellular adenoma and adenoma or carcinoma (combined) in females in all exposed groups, and the incidences of hepatocellular carcinoma in females exposed to 312 or 625 ppm were significantly greater than those in the controls. Also at 2 years, the incidence of hemangiosarcoma in females exposed to 625 ppm was significantly greater than that in the controls. In all exposed groups of males, the incidences of clear cell foci at 15 months were greater than those in the controls; at 2 years, the incidences of eosinophilic foci in all exposed groups of males and the incidences of basophilic and mixed cell foci in males in the 312 and 625 ppm groups were greater than those in the controls. The incidences of mixed cell foci at 15 months in females exposed to 625 or 1,250 ppm and at 2 years in females exposed to 1,250 ppm were also significantly greater than those in the controls. At the end of the 2-year study, increased incidences of cystic degeneration occurred in the liver of all exposed groups of males, and increased incidences of hepatic angiectasis were observed in exposed groups of females.

Incidences of mononuclear cell leukemia in males exposed to 156 ppm and in all exposed groups of females were significantly greater than those in the controls.

Incidences of cataracts in females exposed to 1,250 ppm were greater than those in the controls at the end of the 2-year study.

At the end of the study, there were slight increases in the incidences of testicular interstitial cell adenoma in rats exposed to 312 or 625 ppm.

2-YEAR STUDY IN MICE

Groups of 58 male and 58 female B6C3F$_1$ mice were exposed to 0, 312, 625, or 1,250 ppm tetrafluoroethylene by inhalation for 6 hours per day, 5 days per week, for 95 to 96 weeks. Ten male and ten female mice from each exposure group were evaluated at 15 months for organ weights.

Survival, Body Weights, and Clinical Findings

The survival rates of all exposed groups of males and females were significantly less than those of the controls. Because of the reduced survival due to exposure-related liver neoplasms, the study was terminated during week 96. Mean body weights of exposed groups of males and females were generally similar to those of the controls, except at the end of the study, when they were somewhat less than those of the controls. There were no clinical findings related to tetrafluoroethylene exposure.

Pathology Findings

At the 15-month interim evaluation, there were no differences in absolute or relative kidney, liver, or lung weights between exposed and control groups of mice. At the end of the study, the incidences of multifocal coagulative necrosis of the liver were increased in males in the 625 and 1,250 ppm groups. Also at the end of the study, females in all exposed groups had greater incidences of hematopoietic cell proliferation in the liver than the controls. Angiectasis occurred in all exposed groups of males and females at 15 months and at the end of the study. At the 15-month interim evaluation, hemangiosarcomas were observed in three males exposed to 1,250 ppm and in one female exposed to 312 ppm. The incidences of hemangiosarcoma in all exposed groups of males and females at the end of the study were significantly greater than those in the controls and exceeded the historical chamber control ranges. Also at the end of the study, the incidences of hemangioma in males and females exposed to 312 ppm and in males exposed to 625 ppm were also significantly greater than those in the controls and exceeded the range in historical chamber controls. At 15 months, hepatocellular adenomas and carcinomas occurred in control males and all exposed groups of males and females. Females exposed to 625 or 1,250 ppm had significantly greater incidences of eosinophilic foci than the controls at the 15-month interim evaluation. At the end of the study, the incidences of eosinophilic foci in males exposed to 625 or 1,250 ppm and in females exposed to 312 or 625 ppm were significantly greater than those in the controls. In male and female mice, increased incidences of a variety of hepatocellular neoplasms, including adenomas, multiple adenomas, carcinomas, and multiple carcinomas, were considered related to tetrafluoroethylene exposure.

At the end of the study, the incidences of histiocytic sarcoma (all organs) in all exposed groups of males and females were significantly greater than those in the controls and exceeded the historical control ranges for all organs. The greatest incidences of histiocytic sarcomas were observed in the liver and lung, but these neoplasms were also observed in the spleen, lymph nodes, bone marrow, and kidney.

Significantly increased incidences of renal tubule dilatation (males) and karyomegaly (males and females), located predominantly in the inner cortex, were observed in mice exposed to 625 or 1,250 ppm at 15 months. At the end of the study, the increased incidences of dilatation and karyomegaly in all exposed groups of males and of karyomegaly in 1,250 ppm females were generally significant.

Incidences of hematopoietic cell proliferation in the spleen of all exposed groups of males and females were significantly greater than those in the controls at the end of the study. Additionally, the severity of this lesion increased with increasing exposure concentration.

GENETIC TOXICOLOGY

No increases in the frequency of micronucleated erythrocytes were observed in peripheral blood samples obtained from male and female mice at the end of the 13-week inhalation study of tetrafluoroethylene.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity* * of tetrafluoroethylene in male F344/N rats based on increased incidences of renal tubule neoplasms (mainly adenomas) and hepatocellular neoplasms. There was *clear evidence of carcinogenic activity* of tetrafluoroethylene in female F344/N rats based on increased incidences of renal tubule neoplasms, liver hemangiosarcomas, hepatocellular neoplasms, and mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of tetrafluoroethylene in male and female B6C3F$_1$ mice based on increased incidences of liver hemangiomas and hemangiosarcomas, hepatocellular neoplasms, and histiocytic sarcomas.

Slight increases in the incidences of mononuclear cell leukemia and testicular interstitial cell adenomas in male rats may have been related to exposure to tetrafluoroethylene.

Exposure of rats to tetrafluoroethylene resulted in increased incidences of renal tubule hyperplasia and degeneration in males and females, increased severity of kidney nephropathy in males, and increased incidences of liver angiectasis and cataracts in females. Exposure of mice to tetrafluoroethylene resulted in increased incidences of hematopoietic cell proliferation of the liver in females, liver angiectasis in males and females, renal tubule dilatation in males, renal tubule karyomegaly in males and females, and splenic hematopoietic cell proliferation in males and females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Tetrafluoroethylene

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure Concentrations	0, 156, 312, or 625 ppm	0, 312, 625, or 1,250 ppm	0, 312, 625, or 1,250 ppm	0, 312, 625, or 1,250 ppm
Body Weights	625 ppm group lower than controls	1,250 ppm group slightly lower than controls at end of study	Exposed groups lower than controls at end of study	Exposed groups lower than controls at end of study
Survival Rates	17/50, 12/50, 17/50, 1/50 (2 years)	28/50, 16/50, 15/50, 18/50 (2 years)	38/48, 11/48, 2/48, 1/48 (22 months)	36/48, 4/48, 6/48, 4/48 (22 months)
Nonneoplastic Effects	Kidney (renal tubule): hyperplasia (single sections - 1/50, 1/50, 1/50, 6/50; single and step sections - 7/50, 11/50, 7/50, 24/50); degeneration (2/50, 20/50, 50/50, 49/50); severity of nephropathy (2.3, 1.9, 2.7, 3.5)	Kidney (renal tubule): hyperplasia (single sections - 1/50, 3/50, 6/50, 12/50; single and step sections - 3/50, 6/50, 11/50, 25/50); degeneration (0/50, 0/50, 35/50, 46/50) Liver: angiectasis (0/50, 9/50, 9/50, 14/50) Eye: cataracts (15/50, 4/50, 10/50, 45/50)	Liver: angiectasis (0/48, 6/48, 10/48, 13/48) Kidney (renal tubule): dilatation (0/48, 4/48, 16/48, 36/48); karyomegaly (1/48, 2/48, 10/48, 28/48) Spleen: hematopoietic cell proliferation (14/48, 32/48, 41/46, 42/46)	Liver: hematopoietic cell proliferation (3/48, 19/48, 13/47, 15/47); angiectasis (1/48, 9/48, 6/47, 4/47) Kidney (renal tubule): karyomegaly (0/48, 0/48, 0/47, 38/48) Spleen: hematopoietic cell proliferation (18/48, 39/48, 41/46, 41/47)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Tetrafluoroethylene (continued)

	Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Neoplastic Effects	Kidney (renal tubule): adenoma (single sections - 0/50, 0/50, 6/50, 3/50; single and step sections - 2/50, 4/50, 9/50, 13/50); carcinoma (single sections - 1/50, 0/50, 2/50, 0/50; single and step sections - 1/50, 1/50, 2/50, 0/50); adenoma or carcinoma (single sections - 1/50, 0/50, 6/50, 3/50; single and step sections - 3/50, 5/50, 9/50, 13/50) Liver: hepatocellular carcinoma (1/50, 1/50, 10/50, 3/50); hepatocellular adenoma or carcinoma (4/50, 7/50, 15/50, 8/50)	Kidney (renal tubule): adenoma (single sections - 0/50, 3/50, 1/50, 3/50; single and step sections - 0/50, 3/50, 3/50, 8/50); carcinoma (single sections - 0/50, 0/50, 0/50, 2/50; single and step sections - 0/50, 0/50, 0/50, 3/50); adenoma or carcinoma (single sections - 0/50, 3/50, 1/50, 5/50; single and step sections - 0/50, 3/50, 3/50, 10/50) Liver: hemangiosarcoma (0/50, 0/50, 5/50, 1/50); hepatocellular adenoma (0/50, 4/50, 5/50, 6/50); hepatocellular carcinoma (0/50, 4/50, 9/50, 2/50); hepatocellular adenoma or carcinoma (0/50, 7/50, 12/50, 8/50) Mononuclear cell leukemia: (16/50, 31/50, 23/50, 36/50)	Liver: hemangioma (0/48, 10/48, 5/48, 2/48); hemangiosarcoma (0/48, 21/48, 27/48, 37/48); hemangioma or hemangiosarcoma (0/48, 26/48, 30/48, 38/48); hepatocellular carcinoma (11/48, 20/48, 33/48, 26/48); hepatocellular adenoma or carcinoma (26/48, 34/48, 39/48, 35/48) Hematopoietic system (all organs): histiocytic sarcoma (0/48, 12/48, 7/48, 7/48)	Liver: hemangioma (0/48, 5/48, 2/47, 1/47); hemangiosarcoma (0/48, 27/48, 27/47, 34/47); hemangioma or hemangiosarcoma (0/48, 31/48, 28/47, 35/47); hepatocellular carcinoma (4/48, 28/48, 22/47, 20/47); hepatocellular adenoma or carcinoma (17/48, 33/48, 29/47, 28/47) Hematopoietic system (all organs): histiocytic sarcoma (1/48, 21/48, 19/47, 18/48)
Uncertain Findings	Mononuclear cell leukemia: (34/50, 43/50, 38/50, 31/50) Testis: interstitial cell adenoma (39/50, 40/50, 48/50, 47/50)	None	None	None
Level of Evidence of Carcinogenic Activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic Toxicology				
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:	Negative			